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From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2005/050042	23.03.2005	23.03.2004

International Patent Classification (IPC) or both national classification and IPC
G01N33/68

Applicant
BABRAHAM INSTITUTE

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/050042

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating there has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-38
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-38
Industrial applicability (IA)	Yes:	Claims	1-38
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Re Item V.

1 The following documents were cited in the search report:

D1: WALKER SIMON A ET AL: EMBO (EUROPEAN MOLECULAR BIOLOGY ORGANIZATION) JOURNAL, vol. 23, no. 8, April 2004, pages 1749-1760,

D2: BIVONA TREVER G ET AL:" NATURE (LONDON), vol. 424, no. 6949, 7 August 2003, pages 694-698,

D3: LOCKYER P J ET AL: CURRENT BIOLOGY, CURRENT SCIENCE, GB, vol. 11, no. 12, 2001, pages 981-986,

D4: WALKER S A ET AL:FEBS LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 546, no. 1, 3 July 2003, pages 6-10,

D5: WALKER SIMON A ET AL: JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 277, no. 50, 13 December 2002, pages 48779-48785,

D6: CULLEN P J ET AL: NATURE REVIEWS MOLECULAR CELL BIOLOGY, MACMILLAN MAGAZINES, LONDON, GB, vol. 3, no. 5, May 2002, pages 339-348,

D7: LOGAN-SMITH MELANIE J ET AL: JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 276, no. 50, 14 December 2001, pages 46905-46911,

D8: WO 2005/003783

D9: US-B1-6 514 709

2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.
Document D2 discloses (see pages 696-698): that Ras is activated on and transmits signals from the Golgi apparatus as well as the plasma membrane but the mechanism of compartmentalized signalling was not determined. Here we show that, in response to Src-dependent activation of phospholipase Cgamma1, the Ras guanine nucleotide exchange factor RasGRP1 translocated to the Golgi where it activated Ras. Whereas Ca2+ positively regulated Ras on the Golgi apparatus through RasGRP1, the same second messenger negatively regulated Ras on the plasma membrane by means of the Ras GTPase-activating protein

CAPRI. Ras activation after T-cell receptor stimulation in Jurkat cells, rich in RasGRP1, was limited to the Golgi apparatus through the action of CAPRI, demonstrating unambiguously a physiological role for Ras on Golgi.
Document D6 discloses the integration of calcium and RAS signalling, and mentions Capri, a calcium promoted Ras activator (see page 344 and figure 3):
The method of claim 1 appears to be anticipated by the disclosures in the documents D2 and D6, thus the subject-matter of claim 1 is not novel.

3 The dependent claims 2-6, 8-18 and 34-38 D1 not contain a novel or inventive concept per se and D1 not therefore fulfil the requirements of Articles 33(2) and (3) PCT.

4 The above comments (see item 2), also apply to independent claims 7, 19, 20 21, 22, referring to preferred embodiments of the method of claim 1, and to the claims dependent thereon.

Re Item VI.

D8: WO 2005/003783, from the same inventors, (priority date 26.06.03; filed 26.4.04; published 13.1.05) is relevant prior art under Rule 33.1 © PCT.
The document D1, EMBO Journal, vol.23, no.8, 1 April 2004 (online), pages 1749-1760, discloses the identification of a Ras GTPase-activating protein regulated by receptor-mediated Ca2+ oscillations.
This document, therefore, would appear to disclose or make obvious the subject-matter of claims 1-38.
However, it is assumed that the priority of the present application is validly claimed.
The present priority date of 23.3.04 is, namely, before the publication date of 1.4.04,